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(54) Method for the production of oral dosing units

In order, in a method for the production of oral dosing units with a high content of alkaline action constituents in a form resistant to gastric juice and soluble in the small intestine, to increase the stability of the protective film, resistant to gastric juice, covering the dosing unit, it is proposed that an acid insulating layer is applied to the dosing units in a first work stage and in a second work stage a lacquer coating resistant to gastric juice is applied, the acid insulating layer containing as principal component water-soluble cellulose ethers, preferably hydroxypropyl methyl cellulose, and the acid insulating layer in addition consisting 15% - 30% of a water-soluble, solid, crystalline, non-volatile, pharmacologically acceptable mono- or multi-basic organic acid and 5% - 15% of a water-soluble plasticiser, based on the quantity of the cellulose ethers.

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Claims :

1. Method for the production of oral dosing units with a high content of alkaline action constituents in a form resistant to gastric juice and soluble in the small intestine, characterised in that in a first work stage an acid insulating layer and in a second work stage a lacquer coating resistant to gastric juice are applied to the dosing units, the acid insulating layer containing as principal component water-soluble cellulose ethers, preferably hydroxypropyl methyl cellulose, and the acid insulating layer in addition containing 15% to 30% water-soluble, solid, crystalline, non-volatile, pharmacologically acceptable mono- or multi-basic organic acid and 5% to 15% water-soluble plasticiser, based on the quantity of the cellulose ethers.

2. Method according to Claim 1, characterised in that the organic acids *(sic)* is citric acid, tartaric acid, maleic acid, fumaric acid, succinic acid, adipic acid, suberic acid, malic acid or ascorbic acid or a mixture of two or more of these acids.

3. Method according to Claims 1 or 2, characterised in that the acid insulating layer contains 20% citric acid and 10% glycerol based on the quantity of the cellulose ethers.

4. Method according to one of the previous claims, characterised in that the acid insulating layer is applied in a quantity of 2 mg to 6 mg/cm^2 surface area of the dosing unit.

5. Method according to one of Claims 1 – 4, characterised in that a mixture of equal parts by weight of methanol and dichloromethane or ethanol and dichloromethane or 60% aqueous ethanol is used as solvent for the acid insulating layer, the solid content of the solution being 5% to 10%.

6. Method according to one of the previous claims, characterised in that the lacquer coating resistant to gastric juice consists of a semi-ester of cellulose derivatives with multi-basic carboxylic acids, preferably hydroxypropyl methyl cellulose phthalate with an addition of 15% to 25% based on the semi-ester of the cellulose derivative of a pharmacologically acceptable plasticiser, e.g. phthalic acid esters with primary C_1-C_4 alcohols or acetylated citric acid trialkyl esters with primary C_2-C_4 alcohols, preferably dibutyl phthalate or acetyl citric acid tributyl esters.

7. Method according to one of the previous claims, characterised in that the lacquer coating resistant to gastric juice is applied in a quantity of 5 mg to 12 mg/cm^2 surface area of the dosing unit.

8. Method according to one of the previous claims, characterised in that a mixture of equal parts by weight ethanol and dichloromethane or ethanol and acetone and water in a weight ratio of 8:1:1, the solid content of which is between 5% and 10%, is used as solvent of the lacquer coating resistant to gastric juice.

9. Method according to one of the previous claims, characterised in that the weight ratio of acid insulating layer to lacquer coating resistant to gastric juice is 0.5 to 2, to 2.5 to 5.

10. Method according to Claim 3, characterised in that the solution used for the production of the insulating layer has the following composition :

hydroxypropyl methyl cellulose 50 mPa.s (e.g. Methocel^R 50)	0.250
hydroxypropyl methyl cellulose 15 mPa.s (e.g. Methocel^R 15)	1.750
hydroxypropyl methyl cellulose 5 mPa.s (e.g. Methocel^R 5)	3.000
citric acid	1.000
glycerol, anhydrous	0.500
ethanol	56.100
water	37.400
	100.000

11. Method according to one of Claims 1, 2 or 4 to 9, characterised in that the solution used for the production of the acid protective layer has the following composition :

hydroxypropyl methyl cellulose 15 mPa.s (e.g. Methocel 15^R)	3.000
hydroxypropyl methyl cellulose 5 mPa.s (e.g. Methocel 5^R)	2.000
tartaric acid	1.000
propanediol (1,2)	1.000
ethanol	46.500
dichloromethane	46.500
	100.00

12. Method according to one of Claims 1, 2 or 4 to 9, characterised in that the solution used for the production of the acid protective layer has the following composition :

hydroxypropyl methyl cellulose 15 mPa.s (e.g. Methocel 15[R])	3.00
hydroxypropyl methyl cellulose 5 mPa.s (e.g. Methocel 5[R])	4.00
citric acid	1.50
propanediol (1,2)	1.50
ethanol	45.00
dichloromethane	45.00
	100.00

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Specification :
Method for the production
of oral dosing units

The invention relates to a method for the production of oral dosing units with a high content of constituents with an alkaline action in a form resistant to gastric juice and soluble in the small intestine.

Certain illnesses and/or therapeutic measures make it necessary to give patients daily over a long period of time alkaline-acting substances, for example sodium carbonate. This is successful only by parenteral administration as a spray or infusion. Oral application is therefore excluded because it is immediately neutralised by the hydrochloric acid content of the gastric juice of the alkaline-reacting constituent. On addition of very large quantities of the orally administered, alkaline-reacting substance, ultimately the entire stomach hydrochloric acid would be neutralised, so that firstly the acid protective barrier to microbial infections of the digestive tract is lost, secondly as a result of the body's own regulatory mechanism, the stomach is stimulated to increased hydrochloric acid production, which in turn can lead to stomach ailments.

In order to be able to deal with the daily required parenteral application with its problems and known potential complications - e.g. infections at the puncture point of the injection or infusion - oral application of the dosing unit with a high content of alkaline-reacting constituents is required. The alkaline-reacting constituents must be protected from the effect of the acid gastric juice, but be dissolved in the neutral to weakly alkaline area of the duodenum and be available for resorption.

There therefore exists the problem of providing an alkaline-reacting dosing unit with a coating which on the one hand is insoluble in the acid environment of the stomach, but on the other hand dissolves in the neutral to weakly alkaline area of the duodenum.

Polymer film formers which meet this requirement, e.g. semi-esters of cellulose derivatives with multi-basic acids, such as cellulose acetate phthalate (CAP), cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose acetate succinate (HPMC-AS), ethyl carboxymethyl cellulose (ECMC) or synthetic polymers or copolymers of acrylic acids and acrylic acid esters (Eudragit), ethylene maleic acid alkyl semi-ester copolymers, methylvinyl ether maleic acid alkyl semi-ester copolymers, have been known for many years.

These film formers are characterised in that they are insoluble in strongly acid aqueous environments, but dissolve in weakly acid to weakly alkaline aqueous environments as a result of the ionisation of the free carboxyl groups.

If oral dosing units with a high content of alkaline-reacting constituents are coated with a layer of the above-mentioned polymer film formers, digestive juice resistance and small intestine solubility are expected. It has been shown, however, that the oral dosing units treated in this way with a high content of alkaline-reacting constituents are not definitely resistant to gastric juice but decompose in the acid-reacting digestive juice, as a result of which the therapeutic effect of the pharmaceutical is destroyed. As a result of traces of moisture which penetrate the dosing unit either in film coating, through inappropriate storage or in the acid-aqueous environment of the gastric juice, the free carboxyl groups of the polymer film former are ionised by the alkaline-reacting constituents, so that the film former is water-soluble. Further penetration of water then dissolves large quantities of the alkaline constituents, so that the entire film coating is dissolved.

The problem of the invention is to develop a method which makes it possible to guarantee the stability of dosing units with a coating resistant to gastric juice and soluble in the small intestine even if the dosing unit takes up alkaline-acting constituents.

This problem is resolved according to the invention in the method described at the beginning in that in a first work stage an acid insulating layer and in a second work stage a lacquer coating resistant to gastric juice are applied to the dosing units, the acid insulating layer containing as principal component water-soluble cellulose ethers, preferably hydroxypropyl methyl cellulose, and the acid insulating layer in addition containing 15% to 30% water-soluble, solid, crystalline, non-volatile pharmacologically acceptable mono- or multi-basic organic acid and 5% to 15% water-soluble plasticiser based on the quantity of the cellulose ethers.

Dosing units include in the context of the present application all solid, orally applicable units, for example soft capsules and hard capsules made of gelatine with or without additions of other gel formers, capsules made of other pharmacologically acceptable materials, e.g. water-soluble, heat-gellable cellulose ethers, (meth-)acrylic acid-(meth-) acrylic acid ester copolymers, starch, pullulan, alginates, chitin and other film-forming polymer carbohydrates and/or the derivatives thereof, together with tablets, sugar dragées, film dragées, pills or wafer capsules.

The following acids can advantageously be used as water-soluble, solid, crystalline, non-volatile, pharmacologically acceptable mono- or multi-basic organic acids :

citric acid, tartaric acid, maleic acid, fumaric acid, succinic acid, adipic acid, suberic acid, malic acid, ascorbic acid. The use of citric acid is preferred.

It is particularly advantageous if the acid insulating layer contains 20% citric acid and 10% glycerol based on the quantity of the cellulose ethers. Preferably the acid insulating layer is applied in a quantity of 2 mg to 6 mg/cm^2 surface area of the dosing unit.

It can be provided for that a mixture of equal parts by weight of methanol and dichloromethane or ethanol and dichloromethane or 60% aqueous ethanol is used as solvent for the acid insulating layer, the solid content of the solution being 5% to 10%.

The lacquer coating resistant to gastric juice consists preferably of a semi-ester of cellulose derivatives with multi-basic carboxylic acids, preferably hydroxypropyl methyl cellulose phthalate, with an addition of 15% to 25% based on the semi-ester of the cellulose derivative of a pharmacologically acceptable plasticiser, e.g. phthalic acid esters with primary C_1-C_4 alcohols or acetylated citric acid trialkyl esters with primary C_2-C_4 alcohols, preferably dibutyl phthalate or acetyl citric acid tributyl esters.

It is favourable if the lacquer coating resistant to gastric juice is applied in a quantity of 5 mg to 12 mg/cm^2 surface area of the dosing unit.

It can be provided for that a mixture of equal parts by weight of ethanol and dichloromethane or ethanol and acetone and water in a weight ratio of 8:1:1, the solid content of which is between 5% and 10%, is used as solvent of the lacquer coating resistant to gastric juice.

The weight ratio of acid insulating layer and lacquer coating resistant to gastric juice is preferably 0.5 to 2.0, to 2.5 to 5.0.

It has in fact already been attempted to coat soft gelatine capsules or hard gelatine capsules with a first lacquer coating which does not yet produce any resistance to gastric juice, and arrange a lacquer coating resistant to gastric juice on this first one. German Patent Application P 23 40 060.4 describes a process with which the embrittlement of soft gelatine capsules should be prevented after coating with aqueous Eudragit-L dispersion. This is achieved by applying as a first coating (insulating layer) the Eudragit-E lacquer resistant to gastric juice. The gastric juice resistance is then achieved by applying the Eudragit-L resistant to gastric juice as second layer.

A lacquer coating made of a mixture not resistant to gastric juice of cellulose acetate phthalate, hydroxypropyl cellulose and polyvinylpyrrolidone which should produce a solid anchoring of the second coating resistant to gastric juice made of cellulose acetate phthalate, has been applied to hard gelatine capsules (P 19 24 647.0-41).

In a similar application, a first layer of polyvinylpyrrolidone and a second layer of a coating, resistant to gastric juice, of cellulose acetate phthalate is applied to a hard gelatine capsule (GB 1 190 387).

It has however been shown that a pre-coating produced and applied in this way is not able to improve the gastric juice resistance, i.e. the protective effect is insufficient. This is for example the case with the following substances :

polyvinylpyrrolidone, water-soluble cellulose ethers, e.g. methyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, hydroxymethyl methyl cellulose, shellac singly or in mixture without or together with pharmacologically acceptable plasticisers, e.g. polyethylene glycols, 1,2-propanediol, glycerol, glycerol triacetate, phthalic acid methyl esters, phthalic acid ethyl esters, phthalic acid butyl esters, acetylated or non-acetylated citric acid triethyl or tributyl esters, dissolved in a suitable solvent such as e.g. methanol, ethanol, isopropanol, acetone, methylene chloride, water, singly or in mixture.

It has, however, quite surprisingly been found that a small addition of water-soluble, solid, crystalline, non-volatile, pharmacologically acceptable mono- or multi-basic organic acids to this pre-coating leads to a dosing unit which is definitely resistant to gastric juice and soluble in the small intestine even with a high content of alkaline-acting constituents.

The acid pre-coating (first protective layer) and the coating resistant to gastric juice can be applied with all normal processes in pharmaceutical technology, e.g. in fluidised bed equipment (Glatt, Glatt-Wurster, Aeromatic), in perforated coating pans (Driacoater, Accela-Cota, Hi-Coter) or in standard coating pans, e.g. using the dip pipe.

The lacquer is sprayed in the form of a solution with up to 10% solid, it being possible to use both two-fluid nozzles with compressed air and airless spray guns.

Because of the known thermal instability of the $NaHCO_3$, the use of higher temperatures should be avoided in film coating. Thus 40°C should not be exceeded.

The present invention is illustrated by means of the following examples, without limiting the scope of the invention :

<u>Example 1 :</u>

Soft gelatine capsules size 16 minim oblong which have been produced using the Scherer rotary die process, contain 750 mg sodium hydrogen carbonate in oily content. The surface area of a capsule is 7.0 cm^2. 25,000 of the soft gelatine capsules described are coated to make them resistant to gastric juice in a GLATT fluidised bed device WSG 15.

The capsules are sprayed with 10.0 kg of a lacquer coating solution of the following composition to produce the insulating layer :

hydroxypropyl methyl cellulose 50 mPa.s (e.g. Methocel® 50)	0.250
hydroxypropyl methyl cellulose 15 mPa.s (e.g. Methocel® 15)	1.750
hydroxypropyl methyl cellulose 5 mPa.s (e.g. Methocel® 5)	3.000
citric acid	1.000
glycerol, anhydrous	0.500
ethanol	56.100
water	37.400

	100.00

The lacquer coating solution is sprayed at a rate of approx. 320 g/min using a two-fluid nozzle with a bore size of 1.2 mm at a compressed air pressure of 4 – 6 bar, at a feed air temperature of 36° to 38°C. The capsules receive an insulating layer of 26.0 mg, corresponding to 2.70 mg lacquer dry weight / cm^2 capsule surface area.

Without interrupting spinning, after washing out the nozzle with approx. 0.5 litres of a solvent mixture consisting of equal parts by weight ethanol and dichloromethane, the second lacquer layer resistant to gastric juice is applied. To do this, 17.500 kg lacquer solution of the following composition is spray-applied under the same conditions at a spray rate of 350 g/min :

hydroxypropyl methyl cellulose phthalate (e.g. HP 55®)	5.000
dibutyl phthalate	1.000
ethanol	47.000
dichloromethane	47.000

	100.000

This corresponds to a quantity of 42.0 mg lacquer dry weight per capsule or 6.0 mg/cm^2 capsule surface area.

After expelling the residual solvent, the capsules are resistant to gastric juice for 2 hours according to the standardised test methods of DAB 8, the Eur. Pharm. and USP and degrade in the synthetic intestinal juice and in phosphate buffer with a pH of 6.8 within 10 minutes. The capsules exhibit excellent storage stability, and even after 2½ years there is no evidence of any dissolving phenomena of the protective layers.

Example 2 :

Hard gelatine capsules of size 0, e.g. Scherer-STAR-LOCK[R] capsules, are filled with a powder mixture of the following composition on a normal hard gelatine capsule filling machine :

sodium hydrogen carbonate	0.750 g
magnesium stearate	0.035 g
Aerosil 200	0.015 g

	0.800 g

The capsules are then polished very carefully to remove dust material from the surface of the capsules.

80,000 such hard gelatine capsules are coated in a Driacoater 1200 to make them resistant to gastric juice. The surface area of the capsules is 5.15 cm^2.

To produce the insulating layer, the capsules are sprayed with 34.286 kg of a lacquer solution of the following composition :

hydroxypropyl methyl cellulose 15 mPa.s (e.g. Methocel 15[R])	3.000
hydroxypropyl methyl cellulose 5 mPa.s (e.g. Methocel 5[R])	2.000
tartaric acid	1.000
propanediol (1,2)	1.000
ethanol	46.500
dichloromethane	46.500

	100.000

The perforated pan of the DRIACOATER rotated at 8 rpm. The feed air blown through the bed of the capsules had a temperature of 40°C. A Walther airless spray system was used for spraying the lacquer solution with a nozzle no. 711 and 3.5 bar compressed air pressure for the airless pump. 450 g lacquer solution per minute were applied under these conditions. The capsules receive a 30 mg insulating layer, corresponding to 5.83 mg lacquer dry weight / cm^2 capsule surface area.

Without interrupting rotation or the air current, after changing the airless pump and washing out the nozzle with approx. 0.5 litres of a solvent mixture composed of equal parts by weight ethanol and dichloromethane, the second lacquer layer resistant to gastric juice is applied. Under the same conditions as described previously, 64.000 kg lacquer solution of the following composition is spray-applied :

hydroxypropyl methyl cellulose phthalate (e.g. HP55^R)	6.25
acetyl citric acid tributyl ester (e.g. Citroflex A 4^R)	1.25
ethanol	74.00
acetone	9.25
water	9.25
	100.00

This corresponds to a quantity of 60 mg lacquer dry weight per capsule or 11.65 mg/cm^2 capsule surface area.

The capsules are resistant to gastric juice for two hours according to the standardised test methods of DAB 8, the Eur. Pharm. and USP and dissolve in synthetic intestinal juice and in phosphate buffer with a pH of 6.8 within 15 minutes. The capsules exhibit excellent storage stability, and even after 2½ years there is no evidence of dissolving phenomena of the protective layers.

Example 3 :

Oblong tablets are produced by forming a granule-powder mixture of the following composition :

sodium hydrogen carbonate)	granulated with	0.750
maize starch)	gelatine slime	0.075
talcum (powder)		0.075
		0.900

The surface area of the oblong tablets is 6.1 cm^2.

25,000 oblong tablets are coated to make them resistant to gastric juice in a conventional pear-shaped coating pan with built-in baffle plates using a Boehringer-Strunck dip pipe device.

The oblong tablets are previously insulated with 1 mg shellac per cm^2. To do this, 3.050 kg of the following lacquer solution are spray-applied :

shellac, wax-free	5.00
ethanol	95.00
	100.00

Coating is carried out under the following conditions :

A feed air current of 500 m^3 / hour at a temperature between 39°C and 41°C is passed at a pan rotation rate of 30 rpm through the dip pipe into the bed of the oblong tablets. The lacquer is spray-applied at a rate of 100 g/min by means of a two-fluid nozzle with a bore size of 0.8 mm. The compressed air pressure at the two-fluid nozzle is set at 2.5 bar.

After a short drying phase of 5 minutes, 9.150 kg of the acid insulating lacquer of the following composition is applied without changing the coating parameters and without any intermediate cleaning of the nozzle :

hydroxypropyl methyl cellulose 15 mPa.s (e.g. Methocel 15[R])	3.00
hydroxypropyl methyl cellulose 5 mPa.s (e.g. Methocel 5[R])	4.00
citric acid	1.50
propanediol (1,2)	1.50
ethanol	45.00
dichloromethane	45.00
	100.00

This corresponds to a quantity of 36.6 mg lacquer dry weight per oblong tablet or 6.0 mg lacquer dry weight per cm^2 tablet surface area.

After washing out the nozzle with approx. 0.5 litres of a solvent mixture consisting of equal parts by weight ethanol and dichloromethane, the coating layer resistant to gastric juice is applied without a break. To do this, 20.000 kg lacquer solution of the following composition are spray-applied at a spray rate of 200 g/min under conditions which are otherwise the same :

hydroxypropyl methyl cellulose phthalate (e.g. HP 55[R])	5.00
dibutyl phthalate	1.00
ethanol	47.00
dichloromethane	47.00
	100.00

This corresponds to a quantity of 48 mg lacquer dry weight per oblong tablet or 7.87 mg per cm^2 tablet surface area.

After expelling the residual solvent, the oblong tablets are resistant to gastric juice for 2 hours according to the standardised test methods of DAB 8, the Eur. Pharm. and USP and degrade in the synthetic intestinal juice and in phosphate buffer with a pH of 6.8 within 15 minutes. The storage stability corresponds to that of the capsules of Examples 1 and 2.

All percentage and proportional data in this application are percentage by weight and proportion by weight data.